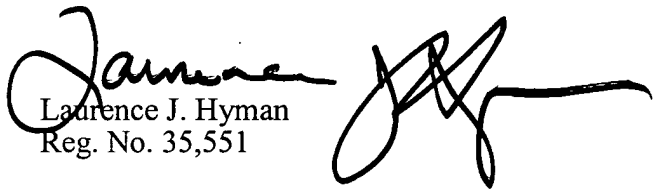
Attached hereto is a marked-up version of the changes made to the Specification by the current Amendment. The attached pages are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

If the Examiner believes a telephone conference would expedite prosecution of this application, he is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 16 of page 8 has been amended as follows:

The term "*Pseudomonas* exotoxin" (PE) as used herein refers to a full-length native (naturally occurring) PE or a PE that has been modified. The full length native sequence of *Pseudomonas* exotoxin can be found in Gray *et al.* (1984) *Proc. Natl. Acad. Sci. USA,* 81: 2645-2649 (*see also* U.S. Patent 5,602,095). A "modified *Pseudomonas* exotoxin" refers to a *Pseudomonas* exotoxin that has an amino acid sequence different than the amino acid sequence of the native *Pseudomonas* exotoxin. Such modifications may include, but are not limited to, elimination of domain Ia, various amino acid deletions in domains II and III, single amino acid substitutions (*e.g.,* replacing Lys with Gln at positions 590 and 606), and the addition of one or more sequences at the carboxyl terminus such as KDEL (SEQ ID NO:9) and REDL (SEQ ID NO:10) (*see* Siegall *et al.*, (1989) *J. Biol. Chem.* 264: 14256-14261). Thus, for example, PE38 refers to a truncated *Pseudomonas* exotoxin composed of amino acids 253-364 and 381-613 (*see* commonly assigned U.S. Patent Application Serial Number 07/901,709 filed June 18,1992). The native C-terminus of PE, REDLK (SEQ ID NO:11) (residues 609-613), may be replaced with sequences such as KDEL (SEQ ID NO:9) and REDL (SEQ ID NO:10). Lys^{590} and Lys^{606} may be each mutated to Gln (see commonly assigned U.S. Patent Application Serial Number 07/522,563 filed May 14, 1990).

Paragraph beginning at line 14 of page 17 has been amended as follows:

When a targeting molecule (*e.g.* a 3B3 antibody) is to be attached to the PE, the PE is preferably one in which Ia (amino acids 1 through 252) substantially or

completely. deleted and amino acids 365 to 380 have been deleted from domain Ib. However all of domain Ib and a portion of domain II (amino acids 350 to 394) can be deleted, particularly if the deleted sequences are replaced with a linking peptide such as GGGGS (SEQ ID NO:12).

Paragraph beginning at line 24 of page 17 has been amended as follows:

For maximum cytotoxic properties of a preferred PE molecule, several modifications to the molecule are recommended. An appropriate carboxyl terminal sequence to the recombinant molecule is preferred to translocate the molecule into the cytosol of target cells. Amino acid sequences which have been found to be effective include, REDLK (SEQ ID NO:11) (as in native PE), REDL (SEQ ID NO:10), RDEL (SEQ ID NO:13), or KDEL (SEQ ID NO:9), repeats of those, or other sequences that function to maintain or recycle proteins into the endoplasmic reticulum, referred to here as "endoplasmic retention sequences" (*see, e.g.,* Chaudhary *et al. Proc. Natl. Acad. Sci. USA* 87:308-312 and Seetharam *et al.* (1991) *J. Biol. Chem.* 266: 17376-17381).

Paragraph beginning at line 7 of page 18 has been amended as follows:

Preferred forms of PE contain amino acids 253-364 and 381-608, and are followed by the native sequences REDLK (SEQ ID NO:11) or the mutant sequences KDEL (SEQ ID NO:9) or RDEL (SEQ ID NO:13). Lysines at positions 590 and 606 may or may not be mutated to glutamine.

Paragraph beginning at page 18, line 10, has been amended as follows:

In a particularly preferred embodiment, the cytotoxin is PE38. PE38 refers to a truncated *Pseudomonas* exotoxin composed of amino acids 253-364 and 381-613 (*see* commonly assigned U.S. Patent Application Serial Number 07/901,709 filed

June 18,1992). The native C-terminus of PE, REDLK (residues 609-613) (SEQ ID NO:11), may be replaced with sequences such as KDEL (SEQ ID NO:9) and REDL (SEQ ID NO:10). Lys^{590} and Lys^{606} may be each mutated to Gln (see commonly assigned U.S. Patent Application Serial Number 07/522,563 filed May 14, 1990).

Paragraph beginning at page 24, line 3, has been amended as follows:

The annealed PCR products are extended using the single stranded DNA as a template (see, for example, MUTAGENE[□]™ mutagenesis protocol, Biorad, Hercules, California, USA). The intact DNA may be used to transform cells and express the new fusion protein. Example 1 provides a detailed description of the preparation of 3B3(Fv)-PE38. The nucleic acid is constructed by spliced PCR using purified individual V_H- and V_L-PCR fragments of 3B3 and cloning them into the *Nde*I-*Hind*III site of pUL17. The vector contains the T7 promoter for expression in Studier's *E coli* BL21(λDE3) expression system (Studier *et al.* (1986) *Mol. Biol.* 189: 113-130).

Paragraph beginning at page 26, line 31, has been amended as follows:

A typical pharmaceutical composition comprising a 3B3 immunotoxin (*e.g.* 3B3-PE38) for intravenous administration would be about 0.1 to 10 mg per patient per day. Dosages from 0.1 up to about 100 mg per patient per day may be used where the drug is well tolerated by the patient. Dosages may be calculated as ranging from 10 [:]μg/kg up to 1 mg/kg, more preferably from about 100 [:]μg/kg up to about 500 [:]μg/kg depending on patient tolerance.

Paragraph beginning at page 35, line 26 and continuing to page 36, line 6, has been amended as follows:

--The most extensively studied chimeric toxin, CD4-PE40, was generated in our laboratory (Chaudhary *et al.* (1988) *Nature* 335: 369-372). It is a recombinant chimeric protein containing, CD4 linked to a 40,000 molecular weight form of *Pseudomonas* exotoxin A. CD4-PE40 was effective in killing an Env expressing cell line and chronically HIV-infected cells (Chaudhary *et al.* (1988) *Nature* 335: 369-372). Also when CD4-PE40 was used in combination with reverse transcriptase inhibitors that block the viral replication cycle, a synergistic effect was observed, leading to elimination of infectious HIV from human T-cell cultures (Ashorn *et al.* (1990) *Proc. Natl. Acad. Sci. USA,* 87: 8889-8893). Based on these data preclinical development of CD4-PE40 was carried out and it was found to be very well tolerated by monkeys so that 250 [:]μg/kg could be administered daily for 10 days without serious toxicity. Subsequently phase I clinical trials were performed (Ramachandran *et al.* (1994) *J. Infect. Dis.* 170: 1009-1013; Davey *et al.* (1994) *Infect. Dis.* 170: 1180-1188). Surprisingly, CD4-PE40 demonstrated very high toxicity in infected patients with a maximum tolerated dose of only 10 [:]μg/kg.

Paragraph at page 36, line 7, has been amended as follows:

The major side effect was liver toxicity. No evidence of anti-HIV effect of this protein in this trial was obtained, probably because of the low amount of the drug that could be given to patients. The toxicity of CD4-PE40 is believed to be due to the CD4 portion directing the immunotoxin to the liver, since we have subsequently given several other recombinant immunotoxins to patients at doses of up to 50 [:]μg/kg without observing dose limiting liver toxicity. In addition a chemical conjugate of PE38 with a whole monoclonal antibody has been given in doses up to 100 [:]μg/kg without liver

toxicity (Pai *et al.* (1996) *Nature Med-* 2:3 50-353). 3B3(Fv)-PE38 is about 20- to 30-fold more effective in killing gp120 expressing and HIV- infected cells *in vitro* than CD4-PE40 and should be devoid of the nonspecific toxicity observed with CD4-PE40.